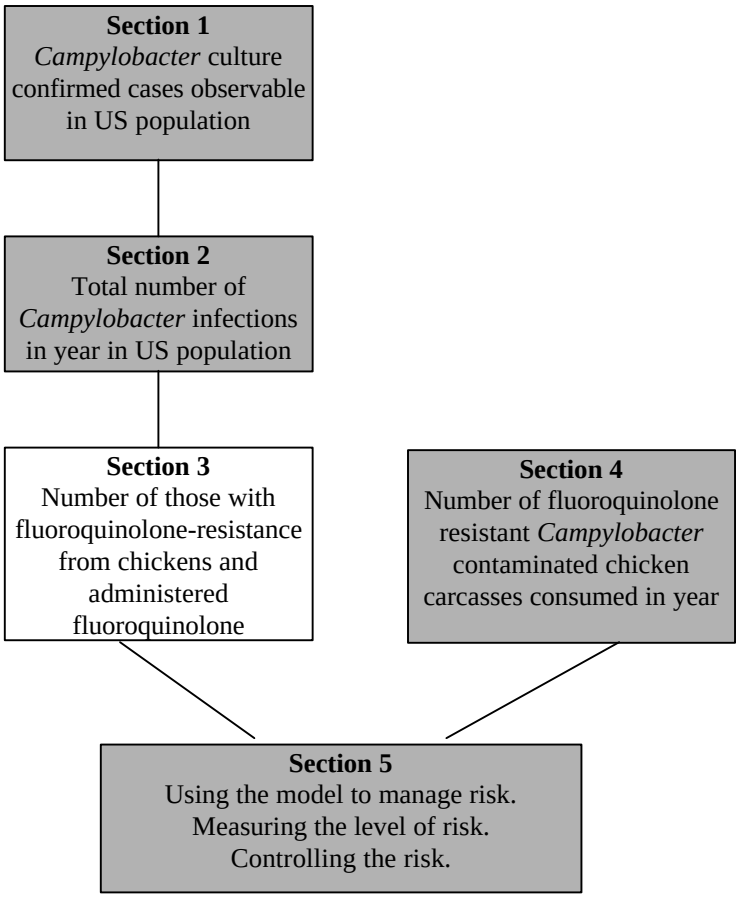
Section 3

Estimate of expected number of people with fluoroquinolone-resistant *Campylobacter* infections from domestically consumed chicken seeking care and receiving fluoroquinolone treatment



Symbol	Description	Formula
$p_{ca\text{-}min}$	Minimum proportion of *Campylobacter* infections relating to domestically consumed chicken	Based on two referenced estimates
$p_{ca\text{-}max}$	Maximum proportion of *Campylobacter* infections relating to domestically consumed chicken	Based on referenced estimate
p_{ca}	Proportion of *Campylobacter* infections relating to domestically consumed chicken	Uniform($p_{c\text{-}min}$, $p_{c\text{-}max}$)
p_{nm}, p_{bm}	Proportion of *Campylobacter* enteric (non-bloody and bloody) illnesses seeking medical care	From Section 2
p_{an}	Proportion of those with non-bloody enteric infection seeking medical care who are treated with a medication	Composite estimate based on data
p_{ab}	Proportion of those with bloody enteric infection seeking medical care who are treated with a medication	Composite estimate based on data
p_{FQ}	Proportion of those who are treated who are prescribed fluoroquinolone	Weighted estimate based on data
p_{rh}	Proportion of *Campylobacter* infections from chicken that are resistant to fluoroquinolone	Weighted estimate based on data
$N3_i$	Estimate of expected number of people with invasive *Campylobacter* infection from chicken for whom fluoroquinolone-resistance resulted in a longer illness	$= N2_i * p_{ca} * P_{FQ} * p_{rh}$
$N3_{eb}$	Estimate of expected number of people with enteric *Campylobacter* infection from chicken with bloody diarrhea for whom fluoroquinolone-resistance resulted in a longer illness	$= N2_{eb} * p_{ca} * p_{bm} * P_{ab} * P_{FQ} * p_{rh}$
$N3_{en}$	Estimate of expected number of people with enteric *Campylobacter* infection from chicken with non-bloody diarrhea for whom fluoroquinolone-resistance resulted in a longer illness	$= N2_{en} * p_{ca} * p_{nm} * P_{an} * P_{FQ} * p_{rh}$
$N3_T$	Estimate of expected total number of people with *Campylobacter* infection from chicken for whom fluoroquinolone-resistance resulted in a longer illness	$= N3_i + N3_{eb} + N3_{en}$

Overview for Section 3.

Epidemiology of campylobacteriosis

Major differences in the epidemiology of common source outbreaks and sporadic cases have been described in the literature (9, 11, 74). The majority of *Campylobacter* cases are classified as sporadic cases (single cases of campylobacteriosis), while outbreaks account for a small proportion of all cases (11). In outbreaks, where a common source was identified, the predominant source of infection was consumption of unpasteurized milk, and less commonly involved contaminated water, or poultry (7, 13, 74). The seasonality of outbreak related disease differs from patterns observed for sporadic disease. Outbreaks peak in May and October while sporadic disease cases occur throughout the year and peak in the summer (43, 74, 75, 76). Evidence of person to person transmission is considered to be low as outbreaks of *C. jejuni* and *C. coli* have rarely been identified in day care or nursing home settings where transmission of disease may be more likely (75, 76). Because outbreaks represent a small number of all cases and the predominant type of infection is sporadic disease, the major focus of this analysis was on risk factors for sporadic disease.

Sporadic campylobacteriosis accounts for more than 99% of all cases (74) and consumption of chicken (11, 22, 29, 31, 36, 37, 71), especially undercooked chicken (24a, 31, 39a) and handling or preparation of raw chicken (37, 39, 44) are the major risk factors identified in epidemiologic investigations. However, one study showed a protective effect when handling or consuming meals prepared from whole chicken (1). Cross-contamination of foods from contaminated poultry has been demonstrated to be associated with certain kitchen practices involved in the preparation of food (31, 44). Other risk factors for sporadic disease identified in the literature are; consumption of contaminated water (63), drinking unpasteurized milk or eating raw milk food products (43), contact with pets or diarrheic animals (1, 64) and travel to developing countries (71).

Campylobacter jejuni is the predominantly isolated *Campylobacter* spp, accounting for more than 90% of human isolates. Other *Campylobacter* spp may cause disease but are not routinely isolated from cases of campylobacteriosis. When methods other than the commonly utilized enrichment techniques are used in the isolation of *Campylobacter*, such as filtration, other species are more commonly found. This indicates that current culture methods are not sufficiently developed to optimize isolation of all species of *Campylobacter*. The lack of knowledge of the magnitude of disease caused by unculturable *Campylobacter* spp potentially creates an unmeasurable impact on the estimate of risk. In this assessment, we have assessed only the measurable risk.

Sources of Infection and Level of Carriage

Campylobacter infections are predominantly foodborne infections associated with animal derived food products (51). *Campylobacter* spp are often found as commensal microbes carried in the intestines of food animals and can contaminate food during slaughter and processing. USDA-FSIS has recently conducted surveys of recovery rates and estimated the mean number per unit (gram, cm^2) of product for some of the major foodborne pathogens found on raw animal products at slaughter and processing. Raw product isolation rates vary by species, with turkeys and chickens appearing to have the highest rates of *Campylobacter* recovery (Table 1.2) (69, 81). Broilers carry the highest carcass and ground product load (Most Probable Number [MPN]/cm^3) of *Campylobacter* when compared to other food animals at slaughter (86, 87) (Table 1.2), consistent with the repeated observations in epidemiologic studies of the increased risk of campylobacteriosis associated with exposure to chicken.

In other surveys of retail food products, *Campylobacter* was isolated from: 2-20% of raw beef; 40% of veal; up to 98% of chicken meat; low proportions in pork, mutton and shellfish; 2% of fresh produce from outdoor markets and 1.5% of mushrooms (23a).

Campylobacter Speciation

In some of the references cited for human campylobacteriosis in this risk assessment the distinction between *C. jejuni* and *C. coli* was not made. *Campylobacter* speciation has been difficult to determine and the methods used to characterize the organisms have changed over time. Currently methods are not standardized. Due to the lack of standardization, laboratories have established unique methods for the identification of *Campylobacter*. This can result in discrepancies between laboratories in speciation (58). Often studies that were published in the literature did not make the distinction between species and when the distinction was made, the studies often relied solely upon biochemical hippurate hydrolysis which does not identify hippurate negative *C. jejuni* (77). Because of the potential for misclassification, additional tests using polymerase chain reaction (PCR) primers to identify the hippuricase gene were added to protocols to identify hippurase negative *C. jejuni*. Recently, PCR based assays have been developed to allow genotypic species characterization. The majority of human disease reported in the United States has been *C. jejuni*, typically comprising over 90% of human isolates (74). The consistently reported preponderance of *C. jejuni* human isolates made the lack of speciation in studies of risk factors less relevant to human campylobacteriosis.

Campylobacter Strains and Epidemiologic Typing Methods

Subtyping of *Campylobacter* strains using phenotypic methods such as biotyping, serotyping, phage typing, and genotypic methods using pulsed field gel electrophoresis, restriction endonuclease analysis, ribotyping, multilocus enzyme electrophoresis (MEE) and PCR fingerprinting have all been used to characterize strains for epidemiologic studies (23). Serotyping has identified similar strains present in *C. jejuni* isolated from chickens, cattle and human cases (57). For serotyped *C. coli* isolates, similar strains have been identified in humans, swine and poultry (57). Using genotypic strain typing methods, similar strains were identified in humans and poultry (23, 46, 59).

Some researchers have proposed that genomic rearrangement may occur in *Campylobacter* (30), suggesting that identification of strains using genotypic methods may have less sensitivity and specificity than was previously thought. However, in laboratory studies genomic instability was not demonstrated in in-vitro and in-vivo tests (30, 94a). Strain typing using a gene, for example the *flaA* and *flaB* genes with PCR-RFLP typing, is considered a sound epidemiologic tool for strain identification (54, 56).

Other Sources of Human Exposure to Campylobacter:

Pet associated cases

Acquisition of puppies and kittens and contact with diarrheic animals has been shown to be associated with human Campylobacteriosis (1, 64). Cats and dogs, especially puppies and kittens have been identified as potential sources of human infections (12, 60). Exposure to diarrheic animals was a risk factor in one study and approximately 6.3% of cases were attributed to this exposure (OR 4.3, 95% CI 1.9 to 9.7). Analysis of isolates obtained from animals and ill persons in the same household indicated the presence of similar Penner serotypes from both sources (64).

Cattle (beef and raw milk) associated cases

C. jejuni is a commensal bacteria inhabiting the intestinal tract of cattle (43). In Canada and Denmark, Penner serotypes and biotypes identified in *C. jejuni* and *C. coli* isolated from cattle were similar to and commonly isolated from human sources (25, 57). In one of the surveys (25) *Campylobacter* spp were recovered from 50% of steers, 40% of bulls and heifers and 22% of cows. Carcasses are contaminated with *Campylobacter* during slaughter and processing and the results of recent estimates of prevalence and load surveys conducted by FSIS are shown in Table 1.2.

Consumption of contaminated milk has often been associated with outbreaks of disease (7, 76). Contamination of milk most often occurs via exposure to feces but mammary excretion of *Campylobacter* has been demonstrated (43, 46). In a survey of Tennessee dairies *C. jejuni* was recovered from 12.3% of bulk tank raw milk samples (43).

A reduction in the number of outbreaks and associated cases has been observed since 1987 when the FDA implemented a ban on the interstate marketing of raw milk (32). The mean annual number of reported outbreaks was much lower for the period after the 1987 ban compared to the period before 1987 (1.3 vs. 2.7) (32). In 1995, for the 28 states that allowed the intrastate sale of raw milk, it was stated that approximately 1% of total milk sold was unpasteurized, although a source for this consumption data was not provided. In Iowa, cases associated with the consumption of raw milk were the result of the ready availability of unpasteurized milk on farms where it was produced, never entering a market (66). The number of reported outbreaks per 10 million person-years in states that allowed the sale of raw milk was 0.14, compared to 0.03 outbreaks per 10 million person-years in states where the sale was illegal (32). It is difficult to assess whether a reduction in disease rates may have changed after the 1987 FDA ban because raw milk consumption data is not readily available and outbreaks associated with exposure to raw milk have not been reported since 1992.

Water associated cases

Contaminated surface water has been associated with human outbreaks, sporadic campylobacteriosis and as a source of infection for animals. In the U.K., a spring was contaminated with *C. jejuni* that was only present when other fecal indicator species were concurrently isolated. The spring was monitored for a 12-month period and some biotypes of the *C. jejuni* strains isolated from the groundwater were identical to strains isolated from a dairy farm located within the same rainwater catchment area (72). Contamination of municipal water sources has been reported and is typically associated with large outbreaks in the community. Drinking water contamination may occur from wild animal reservoirs, especially birds and domestic animal sources by contamination with feces (52, 63).

Isolation of *Campylobacter* from ground water occurs predominantly in the spring and fall. *Campylobacter* in water may be difficult to isolate as they may be present in low numbers, sub-lethally injured by temperature extremes, osmotic stress, nutrient depletion, and by competition from other organisms (49). They may enter a “viable but non-culturable” state but maintain the ability to infect and cause disease in people and animals (49). *Campylobacter* has been isolated from stream water at 4 degrees C for 4 weeks. Isolation was temperature dependent and duration of isolation was less at 25 degrees C compared to 4 degrees C. This indicates that environmental exposures may be temperature dependent and the environment may provide a source of *Campylobacter* that is the result of fecal contamination from animal sources (40).

In a wastewater survey in the Netherlands, three sources of water were tested for the presence of resistant *Campylobacter*. Poultry abbatoir effluent and two sewage purification plants, one receiving mixed sewage from poultry and humans and one not receiving meat-processing sewage, had *Campylobacter* isolated and susceptibility tested. Fluoroquinolone resistance in *Campylobacter* isolates was identified at levels of 29%, 18% and 11% respectively, indicating that water can be a medium for resistant and susceptible *Campylobacter* (66).

Turkey associated cases

The presence of *Campylobacter* in the intestinal tract of turkeys is common. Of 650 cecal samples taken from turkeys on eight farms, 100% were positive for *Campylobacter* and contamination of raw product can occur during slaughter and processing (48). In the King County study, cases exposed to processed turkey sandwich meats demonstrated an increased risk of infection (RR 1.7, 95% CI 1.0 to 2.9) compared to controls. In a companion survey of retail meats, fresh turkey samples were contaminated with *Campylobacter* in 1.8% of samples (31). In a study of members of a Southern California Health Maintenance Organization, a significantly higher proportion of 11 bacteremic cases, not associated with enteric symptoms, compared to 22 controls had consumed processed turkey meat (31, 68). FDA has shown the persistence of *C. jejuni* in processed meat for up to 21 days at 4 degrees C (40, 68). In an USDA-FSIS survey of turkey carcasses (88) and ground turkey (87) the recovery of *Campylobacter* was 90% and 25% respectively. Although the prevalence of carcass isolation was slightly higher than in broilers, the level of contamination of the carcass was lower than the level found on chicken carcasses and approximately half that of the ground product.

Swine associated cases

The majority of *Campylobacter* isolated from swine under currently used microbial species typing is *C. coli* (3, 57) and is usually present in pigs without signs of disease. *C. coli* recovered from swine and typed using Penner serotyping indicated that pig serotypes do not appear to overlap with human: serotypes in Denmark (57), biotypes in the Netherlands (6), and biotypes and serotypes in the United States (53). *C. coli* has been reported to represent approximately 4 and 6 % of human disease in the U.S. and Denmark respectively (19, 57). In studies to determine risk factors for human disease, the finding of an association between human illness and the consumption of pork is rare. One study in Norway identified risk associated with consumption of sausages at a barbecue that could not be attributed to cross-contamination from poultry (44).

Sheep associated cases

Few investigations of *Campylobacter* have been conducted in sheep to determine the frequency of isolation from sheep and sheep food products. Little work characterizing strain serotypes, biotypes or use of genetic typing methods has been reported for ovine associated *Campylobacter* (3, 43).

Shellfish and other associated cases

Few studies have shown an association between disease and exposure to shellfish and other fish (31). *Campylobacter* have been isolated from mushrooms (23a) but little is known of other produce nor the magnitude of human cases from exposures to these sources.

Human to human transmission

The amount of human-to-human transmission of *Campylobacter* is considered to be low and infrequent outbreaks in day care settings and nursing homes confirm the low risk of human to human spread of disease (74).

Fluoroquinolones have been available for human use since 1986 when the first drug was approved in the United States (70, 71). Emergence of fluoroquinolone resistant human *Campylobacter* infections occurred between 1996-8 (71). Although human fluoroquinolone use can lead to the emergence of resistant isolates, human to human transmission of *Campylobacter* is uncommon and is unlikely to contribute to a greater proportion of resistant human infections relative to the contribution of poultry associated resistant infections (70).

Travel Associated Cases

In numerous studies, travel to developing countries has been associated with increased risk of *Campylobacter* infection and since the late 1980's with quinolone resistant *Campylobacter* infections (10, 70, 62)

In the CDC FoodNet *Campylobacter* Case Control Study preliminary results of 580 cases, the proportion of cases that traveled was 12.1%. The level of fluoroquinolone resistance in the travelers was 37.5%, higher than the overall level of resistance in 1998 of 13.3%.

Overview Summary

To summarize, sporadic disease represents the greater proportion of human campylobacteriosis and although many other sources of infection have been determined, consumption of chicken has been the most consistently identified risk factor in epidemiologic studies. Strain typing of isolates has confirmed epidemiologic findings, that similar strains are present in humans and chickens, as well as other animal species. Prevalence surveys indicate a high prevalence and burden of *Campylobacter jejuni* and *C. coli* on chicken carcasses (Table 1.2). *C. jejuni* is isolated from approximately 95% of human cases. The risk assessment question was to determine the measurable impact of fluoroquinolone resistant *Campylobacter* associated with the consumption of chicken on the treatment of human campylobacteriosis. This section determines the number of fluoroquinolone resistant cases attributed to chicken related exposures, (handling, consumption and cross contamination of foods from chicken) that are treated with a fluoroquinolone.

The number of fluoroquinolone resistant cases attributed to chicken related exposures was determined from the total number of cases using the following parameters, (refer to Appendix B for summary reference to mean expected estimates of each parameter):

- Proportion of chicken associated cases
- Proportion of cases seeking care (Bloody diarrhea, Non-bloody diarrhea and invasive cases)
- Proportion of cases receiving antibiotic treatment (Seeking care: no stool submitted for culture; culture confirmed cases: Bloody diarrhea and Non-bloody diarrhea; and invasive cases)

- Proportion of Cases receiving fluoroquinolones (Seeking care: no stool submitted for culture; culture confirmed cases: Bloody diarrhea and Non-bloody diarrhea; and invasive cases)
- Proportion of *Campylobacter* infections from chicken that are fluoroquinolone resistant

Parameter estimations

3.1 (p_{ca}) - Proportion of *Campylobacter* infections relating to domestically consumed chicken: Chicken associated cases (Studies 1-3)

STUDY 1:
A case control study was conducted to explore a wide variety of potential risk factors associated with sporadic campylobacteriosis (travel, food, water, animal and human contacts) and to evaluate the degree to which consumption of various meats played an etiologic role in disease (31). The study was conducted from April 1982 to September 1983 of enrollees in the Group Health Cooperative (GHC), a 320,000 member health maintenance organization located in Western Washington State. Cases and controls were GHC enrollees and residents of King, and southwest Snohomish Counties. Cases were identified as persons from whom *C. jejuni* or *C. coli* was isolated from stool. Cases were excluded if they did not have a telephone, had moved from the study area or did not speak English. Only the first case from each household was included in the study. Cases were matched to controls by age and month of case interview and were interviewed an average of two weeks after onset of symptoms. Of 32 randomly selected controls out of the total number of 526 controls and 90 contacts of controls that were cultured, no enteric pathogens were isolated from either group. Risk factors identified in this study were chicken consumption (relative risk (RR) 2.4, 95% CI 1.6 to 3.6), eating undercooked chicken (RR 7.6, 95% CI 2.1 to 27.6), consumption of Cornish game hen (RR 3.3, 95% CI 1.1 to 9.8), processed turkey meats (RR 1.7, 95% CI 1.0 to 2.9), shellfish (RR 1.5, 95% CI 1.1 to 2.1) and raw or rare fish (RR 4.0, 95% CI 1.1 to 14.5). (Table 3.1)

This study also surveyed practices relating to food preparation surfaces on a "cutting board scale" that ranged from 0-10 points, higher scores indicating safer practices. Controls scored higher on average than cases and a linear trend in risk ($p \leq 0.02$) was associated with decreasing score on the "cutting board scale" that was strongest in chicken consumers and absent in non-chicken eaters. Chicken consumption was quite common in the study population and the estimate of the etiologic fraction, the proportion of cases that would not have occurred had chicken not been consumed, was **48%**. No other fresh red meats or poultry were associated with campylobacteriosis. Another survey conducted in King County was unable to isolate *Campylobacter* from fresh fish and shellfish (31).

This study was limited to cases with enteric illness, submitting stools for culture. The authors indicated a potential non-respondent bias due to lack of participation by controls that may have resulted in a higher estimate of the relative risk (RR 3.0) associated with chicken consumption. The results of this study are now 17 years old and exposures and other factors may have changed in the interim, potentially affecting the level of risk attributable to chickens. Demographic characteristics of the population, the frequency of chicken consumption, the proportion of the population consuming chicken and many other factors may have changed since this study. For example, the amount of chicken consumed has increased since 1982, and in 1998 people consumed 54.4% (72.60/47.02) more chicken, calculated in RTC pounds consumed per capita (80). Because we used this estimate as the lower limit of a uniform distribution and the upper limit was 70%, the current proportion of human campylobacteriosis is likely to be contained within the range.

Table 3.1. Odds Ratios and Etiologic Fraction associated with statistically significant exposure variables for campylobacteriosis, April 1982-September 1983, Group Health Cooperative, King County, Washington (Adapted from Table 4, Ref.64)

Risk Factor	Odds Ratio	95% Confidence Interval	Etiologic Fraction
Chicken Consumption	2.4	1.6-3.6	48.2
Non-household member with enteritis	2.5	1.6-4.0	11.7
Travel to underdeveloped countries	32.9	10.2-133.6	9.0
Household member with enteritis	1.9	1.2-3.0	8.0
Non-home well or surface water	1.8	1.1-2.9	7.6
Any animal with diarrhea	4.3	1.9-9.7	6.3
Raw Milk Consumption	4.6	2.1-10.4	5.2

STUDY 2:

In 1983-1984 at the University of Georgia a case control study was conducted to identify risk factors for *C. jejuni* enteritis (22). Cases were students ill with diarrhea that submitted a stool sample from which *C. jejuni* or *C. coli* was isolated. Controls that were not ill were matched to the cases by sex, residence and age (+/-5years). Interviews were conducted by local public health personnel covering demographic, clinical and other potential exposures. 95 students submitted stools during the fall and winter quarters, all met the case definition and 45 were included in the study. In a breakdown of the 50 exclusions: 27 students were excluded because they could not be contacted, 11 refused to be interviewed, five because a matching control was not found and for seven cases a reason for exclusion was not given. Those excluded from the study did not differ significantly from the included cases based upon date of illness, sex, age, or campus residency.

Overall, 40 cases reported consumption of chicken, 9 undercooked chicken and 11 reported contact with a cat. In an evaluation of the demographic characteristics between the cases and controls, males were at greater risk of infection than female students. One explanation proposed for this difference was that male student cooking practices were less safe than those of the female students.

In univariate analysis of potential risk factors, three statistically significant factors were identified; consumption of chicken within six days of onset of illness (odds ratio=4.7, $p \leq 0.02$), consumption of raw or undercooked chicken (odds ratio=9.10, $p \leq 0.05$) and contact with a cat in the week before onset of illness (odds ratio 9.0, $p \leq 0.05$). Multivariable analysis indicated the same risk factors as in univariate analysis; eating any undercooked chicken (odds ratio 48.7, 95% confidence interval [CI] 2.1 to 1,135), eating any chicken (cooked only) (odds ratio 7.2, 95% CI 1.2-43.7) and contact with a cat (odds ratio 28.2 95% CI 1.02-777) (22). Those who had eaten raw or undercooked chicken were more likely to have eaten barbecued chicken than the cases who had eaten completely cooked chicken. No foreign travel or raw milk consumption was reported by any of the respondents. Illness was not associated with untreated water, contact with a dog or puppy, exposure to another person with diarrhea, consumption of pork, beef, or turkey or place of food preparation. The number of chicken meals consumed by cases peaked in the period two to four days before onset of illness compared to the controls where frequency of consumption was more consistent and only half as frequent as cases. Illness was not associated with preparation of chicken, consumption of chickens cooked whole or the duration between preparation and consumption of chicken. Overall **70%** of cases were attributed to eating chicken and 30% of cases were attributed to contact with cats (74).

Limitations of this study include the lack of representativeness of the study population and the absence of some exposures, such as travel and raw milk that are frequently associated with risk in the population at large. In addition, the study was limited to enteric illnesses because more invasive infections were not eligible for inclusion in the study, although these usually comprise less than 1% of cases. These

differences result in difficulty in generalizing the findings to the United States population but may represent the level of risk in some subgroups of the population.

STUDY 3:
A case control study to identify risk factors for campylobacteriosis was conducted in metropolitan Denver and Fort Collins, Colorado. Hospital and independent laboratories in the region reported all *Campylobacter jejuni* isolations from stools between June 1, and August 15, 1981 to the Department of Health (36). In all, 47 persons with diarrhea and stool cultures positive for *Campylobacter* were matched to controls. Cases were matched to two controls, a "best friend" control and a "nearest neighbor control" by age and sex. A single interviewer conducted telephone interviews within 5-20 days of onset of illness (median 11 days). Questions were asked about potential exposures in the week prior to onset and asked cases about contact with other persons with diarrhea, drinking untreated water, camping, presence of animals in the home, contact with children in diapers and consumption of various food items. Results indicated four risk factors, listed in Table 3.2. An etiologic fraction for consumption of undercooked chicken was calculated at **47.0%** (95% CI 0-75.2%)(95).

Table 3.2. Odds Ratios and Matched Odds Ratios for Exposures in Denver and Fort Collins, Colorado, June 1, to August 15, 1981. (Adapted from Table 1, Ref. 36)

Risk Factor	Odds Ratio	95% Confidence Interval	Matched Odds Ratio	95% Confidence Interval
Undercooked chicken (Chicken eaters only)	2.8	1.0-12.7	6.3	0.9-43.8
Raw Water	3.6	1.0-12.3	10.7	1.9-59.8
Raw Milk	3.3	1.0-10.5	6.9	1.0-46.8
Cats in household	3.1	1.3-7.0	3.2	1.3-8.3

DISCUSSION: In the three case control studies, two indicated an increased risk of infection associated with consumption of chicken, and all three studies indicated an increased risk of campylobacteriosis associated with consumption of undercooked chicken. Two studies also indicated a risk associated with raw milk consumption although the proportion of attributable risk was much less than that attributed to chicken. A similar proportion of disease was attributable to chicken consumption in Studies 1 and 3, approximately 47%. The high estimate of attributable risk, 70% in the university student population indicates in some subgroups of the population that exposures are likely to differ and risk attributable to chicken will vary accordingly. These estimates of the etiologic fraction represent a range of risk that is likely to reflect the degree of risk in the early 1980's. More recent data do not exist for United States populations. Data analysis of a Case Control Study, conducted by the CDC and participating State Health Departments (CA, CT, GA, MD, MN, NY, OR) in 1998, is currently underway and will be published in the near future. The data from this study will provide updated risk factor information from which etiologic fractions associated with identified risk factors may be determined.

ASSUMPTION: The level of risk ascertained in studies in the 1980's represents the current level of risk.

The lower ($p_{ca\text{-}min}$ = 47%) and upper ($p_{ca\text{-}max}$ = 70%) bound estimates were used to model the parameter p_{ca} with a Uniform($p_{c\text{-}min}$, $p_{c\text{-}max}$) distribution. This use of the Uniform distribution reflects a lack of knowledge of the true value of this parameter.

3.2 (p_{nm}, p_{bm}) - Proportion of those with enteric Campylobacteriosis seeking care

In the population survey, described in Section 2.1 Probability of Seeking Care, overall, of those reporting diarrheal illness, a weighted estimate of 12% (61/492) sought care for the illness. The most important factors for seeking care for acute diarrheal disease included having fever, vomiting, "how sick they felt",

stomach cramps, reporting blood in stool and duration of diarrhea. The highest rates for seeking care were amongst children less than 5 years of age, urban residents, and those with health insurance. This estimate was for all diarrheal illness, and not specific to campylobacteriosis.

p_{nm} – *Reported Non-Bloody Stool Rate for Seeking Care*
Of cases with a diarrheal illness and reporting non-bloody stools 12%, a weighted estimate, sought care (59/483) (97).

p_{bm} – *Reported Bloody Stool Rate for Seeking Care*
Of cases with a diarrheal illness and reporting bloody stools 15%, a weighted estimate, sought care (2/4) (97).

In the model, these parameters were set equal to those of Section 2.1. As in Section 2.1, the proportion of those seeking care with invasive infection was estimated at 100%.

3.3 (p_{ab}, p_{an}) - Proportion taking antibiotics for illness
Persons ill with campylobacteriosis may take antibiotics for their illness with or without having sought care. The population survey indicated that 2% of persons that do not seek care take antibiotics (Ref. 35, Table 3). Those cases that seek care present to the physician with varying severity of illness and complicating medical conditions. Cases that were not requested to submit a stool for culture took antimicrobial drugs less commonly than those submitting stools for culture did. Cases of invasive disease represented severely ill patients that were all likely to be prescribed antimicrobial drugs for their illness.

Campylobacter Case Control Study Description, 1998-1999 (97)
A *Campylobacter* case control study was conducted at 7 FoodNet sites in 1998-1999 for a twelve-month period. (The start and end date of the 12-month enrollment period varied between sites). In total, 1314 matched sets of case patients and controls were enrolled in the study. The cases were defined as persons with diarrhea residing in the catchment area with a *Campylobacter* infection identified by a clinical laboratory isolation of *Campylobacter* from stool. Exclusion criteria from the case-control study were persons whose primary residence was outside the catchment area, persons without telephones, persons that were non-English speaking or unavailable for interview (including dead, and non-contactable). Additional exclusion criteria were persons who did not report diarrhea, or who could not recall the date of onset of their diarrhea, or whose onset of diarrhea was >10 days before the date of culture collection, or persons whose infections were outbreak associated; persons were also excluded if another member of the same household had a previous culture-confirmed infection within the past 28 days. A subset of case isolates were tested for antimicrobial susceptibility, either at the CDC (4 sites CA, GA, MD, OR) or by their own state public health laboratory as part of the study (3 sites CT, MN, NY). The number of submissions varied by site and is shown in Section 3.5.

One control per case was interviewed, matched on age and telephone exchange number of the case. Telephone interviews (using progressive and sequential telephone digit dialing based on telephone number of the case) were conducted within seven days of the matched case interview by trained personnel using standardized questionnaires for cases and controls. Questionnaires included questions about demographic characteristics, symptoms of illness, treatment, potentially complicating medical conditions, possible exposures such as travel, foods consumed and hygienic practices. For the seven participating sites during the study period, there were 3860 reported *Campylobacter* cases in surveillance; 2870 were eligible to be in the study (Table 1.2), 1461 cases were enrolled; 1314 were matched with a control, resulting in a 46% (1314/2870) enrollment rate for the case-control study.

Not submitting a stool for culture
In the population seeking care, 40% (**16**/**41**) of persons not requested to submit a stool sample by their health care provider took antibiotics for their illness (approximately 81% of all cases seeking care were not requested and did not provide a stool for culture, Section 2.2).

ASSUMPTION: The population survey proportion of cases of all acute diarrheal illness seeking care, not submitting a stool sample and receiving an antibiotic (40%) is similar to that for persons ill with campylobacteriosis.

Submitting a stool for Culture
Preliminary analysis of the CDC FoodNet *Campylobacter* Case Control Study provided estimates of antibiotic use for culture confirmed cases (97). The proportion of cases treated with antibiotics was 84.4% unweighted estimate (488/578) and a weighted estimate of 85.3%. The individual state treatment rates were CA 91.7% (11/12), CT 84.4% (162/192), GA 93.8% (30/32), MD 90.5% (19/21), MN 82.2% (199/242), NY 86.8% (59/68) and OR 72.7% (8/11) (97).

Invasive Disease
ASSUMPTION: Because of the severity of illness upon presentation, all cases with invasive disease are presumed to take antibiotics for their illness.

DISCUSSION: Severity of illness is one of many factors that lead physicians to prescribe antibiotics to patients with a diarrheal illness.

The parameters p_{an} and p_{ab} are modeled as:

$p_{an} = p_{nc}*y + (1-p_{nc})* z$
$p_{ab} = p_{bc}*y + (1-p_{bc})* z$

where $y = \sum_j W_j Beta(D_j + 1, C_j - D_j + 1)$,

z = Beta(16+1,41-16+1)

and W_j are the weights for FoodNet sites as defined in section 1.9; C_j is the number of culture-confirmed cases for whom it is known whether they received an antibiotic or not for site j; and D_j is the number of culture-confirmed cases who did receive an antibiotic, shown in Table 3.3.

3.4 (p_{FQ}) - Proportion of those who are treated who are prescribed fluoroquinolone

Not seeking care
The 2% of persons with a diarrheal illness in the population survey that do not seek care and take antibiotics are not included in the assessment of fluoroquinolone treatment because they represent a small and unquantifiable fraction of cases.

Not submitting a stool for culture
ASSUMPTION: Patients with campylobacteriosis who did not submit stools were treated by their health care provider with fluoroquinolones at the same frequency as those who submitted stools.

Submitting a stool for Culture (Non-Bloody and Bloody Diarrhea)
In preliminary results from the *Campylobacter* Case Control Study the proportion of cases treated with antimicrobials and receiving fluoroquinolone treatment was 55.5% (271/488) for both crude and weighted estimates. The individual state treatment rates were CA 45.5% (5/11), CT 57.4% (93/162), GA 63.3% (19/30), MD 42.1% (8/19), MN 55.3% (110/199), NY 52.5 % (31/59), OR 62.5% (5/8). (Table 3.3)

Invasive Disease
ASSUMPTION: The proportion of fluoroquinolone prescriptions of total antibiotic prescriptions is the same for patients with invasive campylobacteriosis treated by their health care providers as it is for patients with enteric campylobacteriosis treated by their health care providers.

The parameter p_{FQ} was thus modeled as:

$$p_{FQ} = \sum_j W_j Beta(E_j + 1, D_j - E_j + 1)$$

where, again, the W_j are the FoodNet site weights, E_j is the number of cases receiving fluoroquinolone and D_j is the number of cases receiving antibiotics, shown in Table 3.3.

3.5 (p_{rh}) - Proportion of human *Campylobacter* infections attributable to chickens that are fluoroquinolone resistant

Ciprofloxacin is one of two antimicrobials used to monitor losses of susceptibility to the class of fluoroquinolone drugs in the National Antimicrobial Resistance Monitoring System (NARMS) and represents the most widely used member of the class in human medicine. The breakpoint used, 4 mcg/ml, was formally established for other *Enterobacteriaceae* by NCCLS and is used as a predictor of *Campylobacter* susceptibility to Ciprofloxacin. The breakpoint indicating loss of clinical effectiveness has not been set for fluoroquinolone drug use in *Campylobacter* infections but a breakpoint of 4 mcg/ml is used by many diagnostic labs and surveillance systems to monitor shifts in susceptibility.

E-Test strips (AB BIODISK, Solna, Sweden) contain an antimicrobial gradient on the opposite surface of a scale indicating increasing concentrations of the test drug. Growth along the strip is inhibited where the concentration of the drug exceeds the minimum inhibitory concentration (MIC) of the microorganism being tested. *Campylobacter* E-test MIC's to Ciprofloxacin have been compared with agar dilution susceptibility testing and although the E-Test tended to produce lower results, indicating higher activity than that observed on agar dilution testing, the overall correlation of MIC's between methods was good at 90.4% of the tests in one study (38).

Fluoroquinolone resistance has been significantly associated with human infections that are travel related (61, 71), foodborne, particularly chicken associated infections (71) and treatment of human illness with a fluoroquinolone (67).

580 isolates were obtained from the FoodNet catchment area from cases enrolled in the *Campylobacter* Case Control Study. *C. jejuni* comprised 92.4%, *C. coli* 2.7% and *C.* "other" 4.8% of the total number of isolates. The isolates were cultured and speciated in clinical laboratories and forwarded to the FoodNet State Health Department where susceptibility testing was performed. Isolates (150/580) were forwarded to CDC for National Antimicrobial Resistance Monitoring System (NARMS) surveillance susceptibility testing using E-Test and compared to state health department findings. The correlation of susceptibility testing results between laboratories was good.

The proportion of domestically acquired fluoroquinolone resistant cases that were not potentially attributable to human use of the drug were estimated after removal of cases with exposures associated with travel and fluoroquinolone use prior to culture. In preliminary results from the CDC Case Control Study Resistance Subgroup of 580 cases, 409 remained after removing cases that had taken fluoroquinolones prior to culture, cases for whom it was not known when the fluoroquinolones were taken, and those cases that had traveled in the 7 days prior to onset of disease. Of these cases 6.36% (26/409) of isolates were resistant non-travel associated infections. Because the number of isolates that were susceptibility tested was disproportionately distributed by site and the rate of resistance varied by site, the level of resistance was weighted by the site population size to better represent the relative contributions of each FoodNet site (18). (Number of resistant isolates/Number of Isolates Tested, CA-1/8, CT-11/128, GA-1/21, MD-3/16, MN-4/177, NY-6/49, and OR-0/10 (97).

DISCUSSION: It is difficult to know what proportion of the resistance in human campylobacteriosis may be attributable to a single source of human exposure when a level of resistance is defined in a population of cases whose exposures are multiple and varied. The level of resistance in the population may be consistent across all sources of human infection or may be disproportionately distributed, associated with certain types of exposures carrying higher levels of fluoroquinolone resistance than other sources of human infection.

Fluoroquinolone use has been associated with the development of fluoroquinolone resistance in *Campylobacter* in clinical trials in poultry production units (41), in poultry production in the Netherlands (24) and in the United States (71) after the introduction of veterinary fluoroquinolones.

An Extra Label Use Prohibition of fluoroquinolone use in food-producing animals was published in 1997 (21CFR530.41), limiting food animal drug use to species listed on the product label. Approvals of fluoroquinolone drugs for use in animals include feline and canine oral and canine injectable products (available in 1989), poultry water soluble and in-ovo injectable products (available in 1995) and feedlot cattle injectable products (available in October 1998). There are no fluoroquinolones currently approved for use in swine.

Campylobacteriosis is primarily an animal derived foodborne disease, with the predominant source of human infections attributed to poultry (22, 31, 36, 64). There is little surveillance data available to describe the level of fluoroquinolone resistance in *Campylobacter* isolated from animal derived food and other food products in the United States, either before or after the approval of these drugs for food animal use. Chicken *Campylobacter* isolates collected in 1998 indicated a level of 13% resistance to Ciprofloxacin (see Section 3.1). Because there was no food animal fluoroquinolone use other than use in poultry until late 1998, and no resistance was observed prior to 1992 in human cases[1] it is unlikely that the increase in domestically acquired fluoroquinolone resistance observed in people since 1996[2] can be attributed to a consistently distributed source of resistant *Campylobacter* exposures. Distribution of resistance from foodborne sources is more likely to be associated with specific exposures and limited predominantly to poultry.

[1] In two surveys encompassing 474 human isolates from 1982 to 1992 in the United States, only a single Ciprofloxacin resistant isolate was identified and subsequently speciated as *C. lari* which is intrinsically resistant to fluoroquinolones (70).

[2] After removal of persons who had traveled within 7 days of illness onset and removal of those taking fluoroquinolones prior to culture, quinolone resistance in Minnesota was observed in 0.8% of isolates in 1996 and had increased to 3.0% in 1998 (chi square for linear trend, 9.8; $p \leq 0.002$) (71). In Minnesota quinolone resistance, screened by nalidixic acid disc diffusion was highly correlated with resistance to ciprofloxacin using the E-Test, (sensitivity 99.6%, specificity 98.4%) (71). A survey of *Campylobacter* isolated from 88% of 91 chicken products resulted in *C. jejuni* from 67(74%) and *C. coli* from 19 (21%) of samples and six samples were the source of both pathogens. Products carrying resistant isolates were purchased from 11 stores representing 8 franchises and originated in seven processing plants in five states (70, 71) indicating widespread resistance in chicken *Campylobacter* isolates. Molecular subtyping was performed using PCR restriction endonuclease length polymorphism typing of the flagellin gene in *the C. jejuni* human and chicken product isolates. 12 subtypes were identified from 13 *C. jejuni* positive chicken products. Six of seven resistant subtypes in the chicken products were also identified in the quinolone resistant human isolates. For people acquiring infections during 1997, excluding cases that had taken fluoroquinolones prior to culture, persons with non-traveler resistant infections were more likely to *have C. jejuni* subtype also found in the quinolone resistant *C. jejuni* from chicken products (odds ratio 15.0, 95% CI 1.9 to 321.8) (70).

ASSUMPTIONS: The fluoroquinolone resistance observed in persons ill from campylobacteriosis, (after removal of travelers, those who took a fluoroquinolone prior to culture and those for whom the time of taking the fluoroquinolone was unknown) is largely attributed to chickens.
DATA GAP: Quantification of the proportion of human disease attributable to various sources and the determination of the level of resistance carriage within the specific exposures would more precisely allow the determination of the relative contributions of the various exposures to fluoroquinolone resistant human disease. A model intended to determine the human health impact of the level of resistance in *Campylobacter* attributable to fluoroquinolone use in food animals will need to distribute the burden of resistant human disease amongst many different food animal species and potentially other food sources.

The parameter p_{rh} is thus modeled as[3]:

$$p_{rh} = \sum_j W_j Beta(G_j + 1, F_j - G_j + 1)$$

where G_j is the number of human isolates that tested positive for resistant *Campylobacter* and F_j is the number of human isolates that were tested for resistance, shown in Table 3.4.

3.6 ($N3_{en}$, $N3_{eb}$, $N3_i$) - Estimate of nominal mean number of people with fluoroquinolone resistant enteric and invasive *Campylobacter* infection from chicken who receive fluoroquinolone.

This is the number of persons with fluoroquinolone resistant infections in 1998 that are attributed to exposure to chicken that seek care and are treated with a fluoroquinolone.

Invasive disease

This parameter is estimated as:

$N3_i = N2_i * p_{ca} * p_{FQ} * p_{rh}$

Figures 3.1a and 3.1b show the distribution of the estimated values for 1998 for this quantity. The distribution has the following statistical characteristics:

Model output	5 percentile	Mean	95 percentile
$N3_I$	10.9	19.0	29.5

[3] There is a recognised logical inconsistency in this parameter estimate that has not been corrected in this model. We have removed cases of campylobacteriosis attributable to sources other than chicken. Because resistance was predominantly attributed to chickens, after removal of travellers and prior fluoroquinolone use, the remaining "chicken associated cases" should reflect the level of resistance restricted to the chicken associated cases. This correction will be made in the final revision.

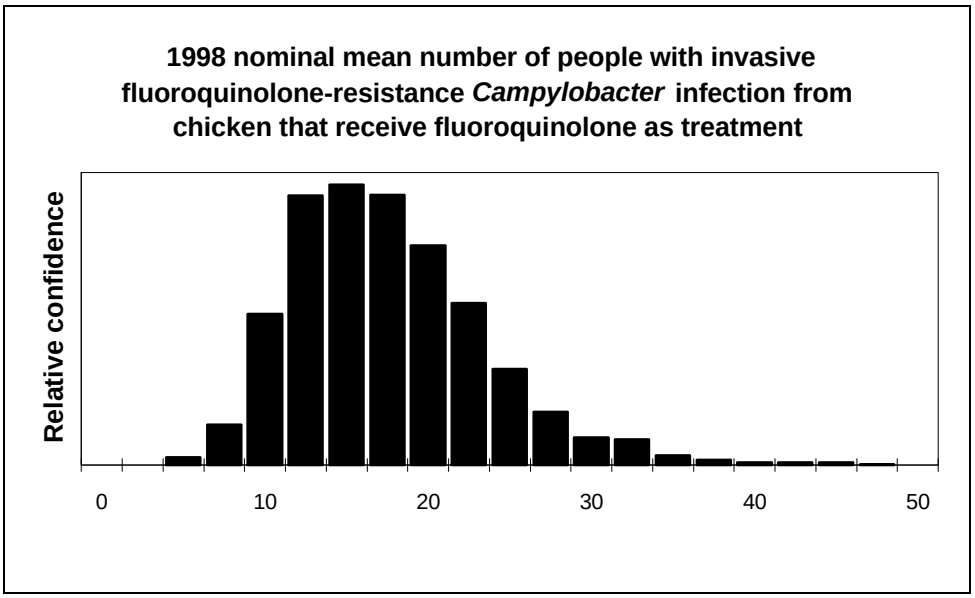


Figure 3.1a. Relative confidence distribution of $\mathbf{N3_i}$. *Note that the vertical axis for this and all other figures showing histogram (relative probability) representations of probability distributions have no scale: this is because the y-axis values are purely a function of the width of the histogram bars and not a fundamental measure of the distribution itself. There is often confusion in interpreting such figures because of the vertical axis values: the reader should consider these figures as a pictorial and intuitive representation of the possible values for the model outputs and the relative confidence one has about these values. The cumulative distribution function figures (S-curves like Figure 3.1b) can be used to read off any required probability measure.*

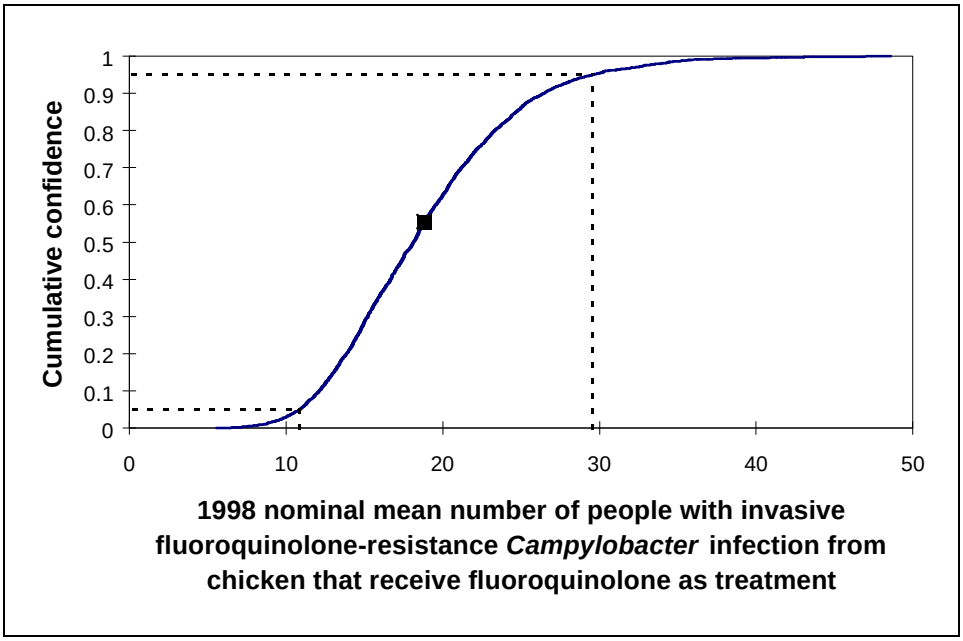


Figure 3.1b. Cumulative confidence distribution of $\mathbf{N3_i}$.

Enteric disease

These parameters are now estimated as:

$\mathbf{N3_{eb}} = N2_{eb} * p_{ca} * p_{bm} * P_{ab} * P_{FQ} * p_{rh}$

$\mathbf{N3_{en}} = N2_{en} * p_{ca} * p_{nm} * P_{an} * P_{FQ} * p_{rh}$

Figures 3.2a, 3.2b, 3.3a, and 3.3b show distributions of the estimated values for 1998 for these two quantities. The distributions have the following statistical characteristics[4]:

Model output	5 percentile	Mean	95 percentile
$\mathbf{N3_{eb}}$	738	1410	2394
$\mathbf{N3_{en}}$	1734	3620	6545

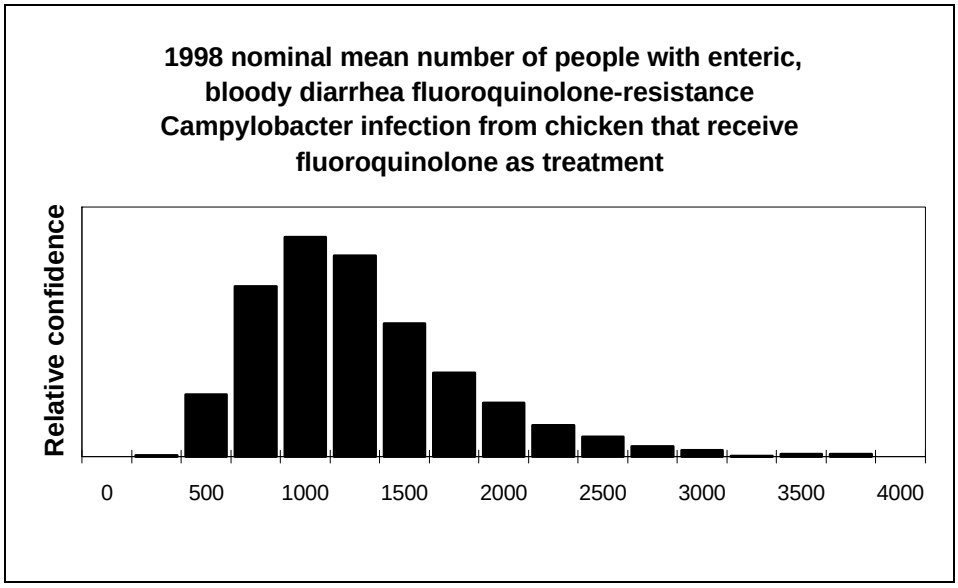


Figure 3.2a. Relative confidence distribution of $\mathbf{N3_{eb}}$

[4] Values incorporated in these tables will vary very slightly from graphed results due to small variations in repeating Monte Carlo simulations. The graphs are based on smaller simulation runs whilst the quoted values are based on large simulations and are thus more accurate.

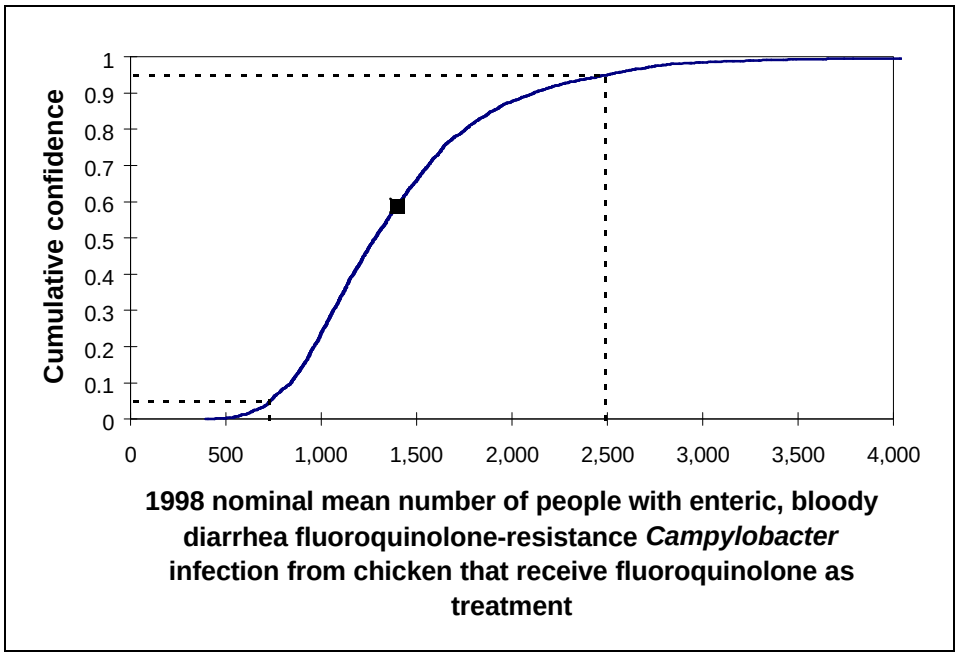


Figure 3.2b. Cumulative confidence distribution of $\mathbf{N3_{eb}}$

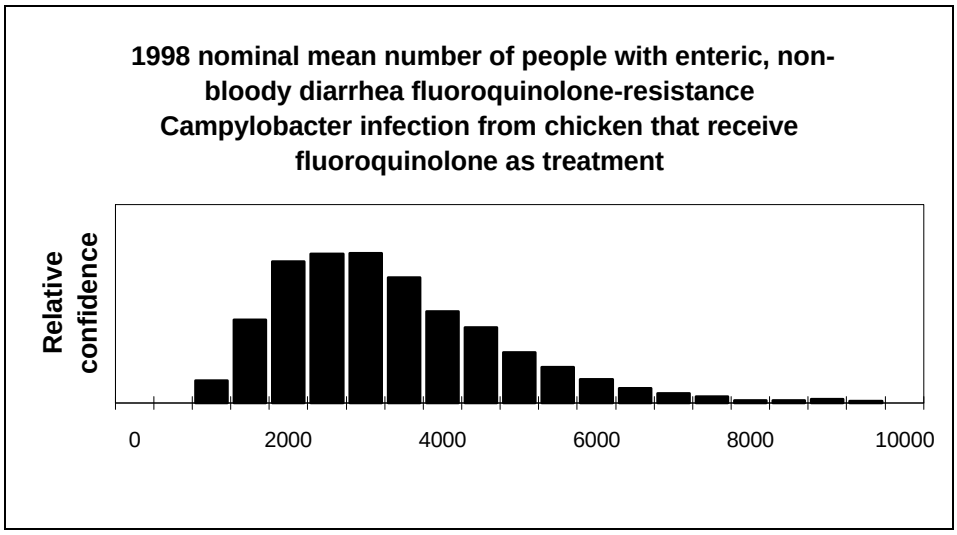


Figure 3.3a. Relative confidence distribution of $\mathbf{N3_{en}}$

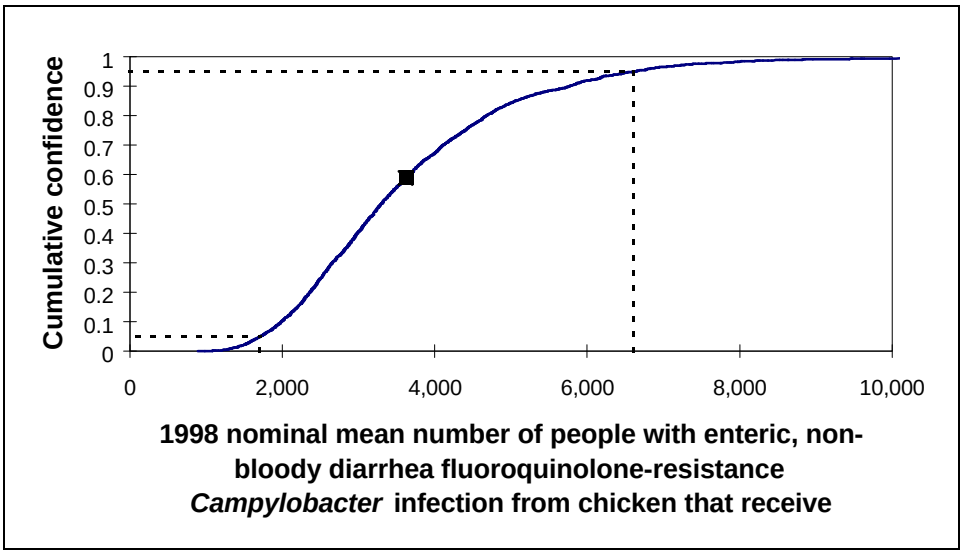


Figure 3.3b. Cumulative confidence distribution of $\mathbf{N3_{en}}$

3.7 ($N3_T$) - Estimate of total nominal mean number of people with fluoroquinolone resistant *Campylobacter* infection from chicken who receive fluoroquinolone.

The distribution of the sum, $\mathbf{N3_T = N3_I + N3_{eb} + N3_{en}}$ is shown in Figures 3.4a and 3.4b. The distribution has the following statistical characteristics.

Model output	5 percentile	Mean	95 percentile
$\mathbf{N3_T}$	2585	5065	8595

Section Summary

The model predicts that in 1998 about 5065 people who had fluoroquinolone resistant *Campylobacter* infections from chicken received fluoroquinolones. A 90% confidence interval for the number of people who had fluoroquinolone resistant *Campylobacter* infections from chicken receiving fluoroquinolones is (2585, 8595). The fairly long length of the confidence interval is reflective of the lack of certainty in the various parameters used in the model up to this point. Relative contributions of the various components of the model to the model uncertainty will be presented in Section 5, Sensitivity Analysis.

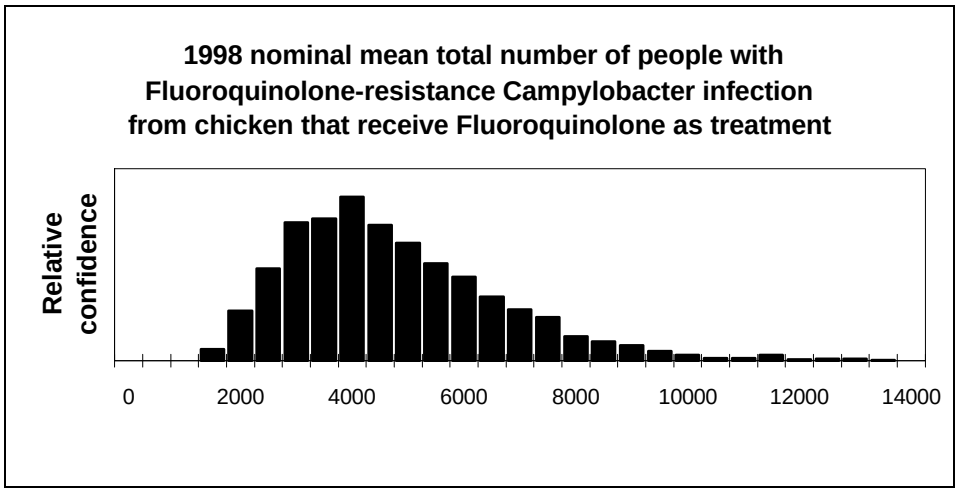


Figure 3.4a. Relative confidence distribution of $\mathbf{N3_T}$.

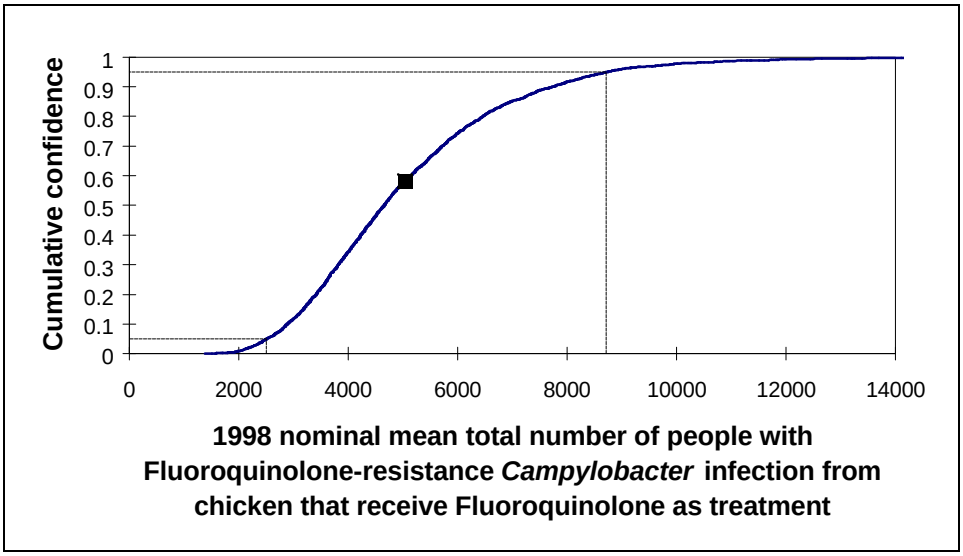


Figure 3.4b. Cumulative confidence distribution of $\mathbf{N3_T}$.

Table 3.3. Numbers of Culture-confirmed Cases with Enteric Campylobacteriosis who Responded when Asked if they had Received Antibiotics; who had Antibiotics, and who had fluoroquinolone, by Site.

Site j	Catchment	Weighting Fraction W_j	Number for whom response was known C_j	Number who were treated with antibiotics D_j	Number who were treated with fluoroquinolone E_j
CA	2,146,096	0.103556	12	11	5
CT	3,274,069	0.157985	192	162	93
GA	3,746,059	0.18076	32	30	19
MD	2,444,280	0.117945	21	19	8
MN	4,725,419	0.228017	242	199	110
NY	1,106,085	0.053372	68	59	31
OR	3,281,974	0.158366	11	8	5
Total	20,723,982	1	578	488	271

Table 3.4. Numbers of Culture-confirmed Cases with Enteric Campylobacteriosis where Campylobacter was Tested for fluoroquinolone Resistance and fluoroquinolone Resistant, by Site.

Site j	Catchment	Weighting Fraction W_j	Number tested F_j	Number fluoroquinolone resistant G_j
CA	2,146,096	0.103556	8	1
CT	3,274,069	0.157985	128	11
GA	3,746,059	0.18076	21	1
MD	2,444,280	0.117945	16	3
MN	4,725,419	0.228017	177	4
NY	1,106,085	0.053372	49	6
OR	3,281,974	0.158366	10	0
Total	20,723,982	1	409	26